# Soft tissue sarcomas of the extremities

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Soft tissue sarcomas are a diverse group of neoplasms that arise in the connective tissues throughout the body. They account for approximately 1% of adult malignancies and 7% to 15% of pediatric malignancies. About 50% to 60% of sarcomas occur in the extremities, and although they are rare, they are responsible for more deaths than testicular cancer, Hodgkin's disease, and thyroid cancer combined (1). These tumors are notorious for recurring and metastasizing—often with devastating results—despite apparently complete resection.

## INCIDENCE

The National Cancer Institute's Cancer Surveillance, Epidemiology, and End-Result (SEER) Program in 1996 reported 6400 new cases of soft tissue sarcoma, including 3500 in males and 2900 in females (2), for a male-to-female ratio of about 1.2:1. Deaths were reported in 1800 males and 1900 females, so although males are more likely to develop sarcoma, females are more likely to die of it.

The 1996 SEER data revealed significant changes from 1990: 700 more new cases and 600 more deaths were reported (3). Devesa studied the decades from the 1970s through the 1990s, however, and observed no such increase (4). This discrepancy may be attributed to the large number of Kaposi's sarcoma cases that were reported in the 1980s and 1990s and included in the SEER data.

Data from the SEER program indicate that African Americans are clearly more predisposed to develop sarcomas than are whites (with the exception of blood vessel sarcomas, which in this scheme included Kaposi's sarcoma) (*Table 1*) (5). The predilection for development of sarcomas in males was shown for all histologic subtypes except stromal sarcomas and leiomyosarcomas. The higher incidence of leiomyosarcomas in females is probably due to the occurrence of uterine leiomyosarcoma.

Approximately 40% of all sarcomas occur in people older than 55 years. The incidence rate in the general population is 1.4 per 100,000 but rises to 8 per 100,000 for people older than 80 years. The distribution of histologic types varies by age. For example, rhabdomyosarcoma is mostly a tumor of the young; synovial sarcoma and fibrosarcoma occur in younger adults; and malignant fibrous histiocytomas occur more often in mature adults (6).

In contrast to the biologic behavior of carcinomas, which varies dramatically depending on the site and therefore the cell type of origin, that of soft tissue sarcomas is similar regardless of

**Table 1. Average annual age-adjusted incidence rates (per 100,000) for soft tissue sarcoma by histologic type, race, and gender\***

| Histology | White | | African American | |
|---|---|---|---|---|
| | Men | Women | Men | Women |
| Blood vessel sarcoma | 6.81 | 0.28 | 5.04 | 0.32 |
| Fibrosarcoma | 1.54 | 1.09 | 1.88 | 1.48 |
| Leiomyosarcoma | 0.80 | 1.10 | 1.22 | 2.01 |
| Sarcoma, NOS | 0.53 | 0.44 | 0.72 | 0.50 |
| Liposarcoma | 0.60 | 0.35 | 0.79 | 0.31 |
| Rhabdomyosarcoma | 0.32 | 0.17 | 0.43 | 0.22 |
| Stromal sarcoma | 0.02 | 0.23 | 0.03 | 0.34 |
| Synovial sarcoma | 0.10 | 0.09 | 0.17 | 0.07 |
| Meningiosarcoma | 0.07 | 0.09 | 0.20 | 0.08 |
| Mesenchymoma | 0.01 | <0.01 | 0.03 | 0.04 |
| Lymphangiosarcoma | <0.01 | 0.01 | — | — |
| Others | 0.35 | 0.67 | 0.23 | 1.06 |
| Total | 11.15 | 4.53 | 10.73 | 6.43 |

\*Reprinted from reference 5.
NOS indicates not otherwise specified.

location. However, the management and therefore the outcome for these lesions are based largely on anatomic location. Thus, a general division of sarcomas into those of the extremities and those of visceral, retroperitoneal, or trunk origin is convenient for discussion. This review focuses primarily on sarcoma of the extremities.

## CLASSIFICATION AND GRADING

Sarcomas are classified according to the type of tissue that they form, not where they arise; thus, a histogenic classification is used. Most connective tissues, if not all, can potentially give rise to either a benign or malignant type of tumor (*Table 2*). According to data from Memorial Sloan-Kettering Cancer Center, the most common sarcoma found in the extremities is malignant fibrous histiocytoma, followed by liposarcoma, synovial

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## Table 2. Histogenic classification scheme for benign and malignant soft tissue tumors*

| Tissue formed (histogenesis) | Benign soft tissue tumor | Malignant soft tissue tumor |
|---|---|---|
| Fat | Lipoma | Liposarcoma |
| Fibrous tissue | Fibroma | Fibrosarcoma |
| Skeletal muscle | Rhabdomyoma | Rhabdomyosarcoma |
| Smooth muscle | Leiomyoma | Leiomyosarcoma |
| Bone | Osteoma | Osteosarcoma |
| Cartilage | Chondroma | Chondrosarcoma |
| Synovium | Synovioma | Synovial sarcoma |
| Blood vessel | Hemangioma | Angiosarcoma |
| Lymphatics | Lymphangioma | Lymphangiosarcoma; malignant hemangio-pericytoma |
| Nerve | Neurofibroma | Neurofibrosarcoma |
| Mesothelium | Benign mesothelioma | Malignant mesothelioma |
| Tissue histiocyte | Benign fibrous histiocytoma | Malignant fibrous histiocytoma |
| Pluripotent | None recognized | Malignant mesenchymoma |
| Uncertain | None recognized | Ewing's sarcoma; alveolar soft parts sarcoma; epithelioid sarcoma |

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## Table 3. Staging of soft tissue sarcomas of the extremities*

**Stage Grouping**

| | | | | | | |
|---|---|---|---|---|---|---|
| Stage I | T1a, 1b, 2a, 2b | N0 | M0 | G1–2 | G1 | Low |
| Stage II | T1a, 1b, 2a | N0 | M0 | G3–4 | G2–3 | High |
| Stage III | T2b | N0 | M0 | G3–4 | G2–3 | High |
| Stage IV | Any T | N1 | M0 | Any G | Any G | High or Low |
| | Any T | N0 | M1 | Any G | Any G | High or Low |

**Definition of TNM**

*Primary Tumor (T)*
TX   Primary tumor cannot be assessed
T0   No evidence of primary tumor
T1   Tumor 5 cm or less in greatest dimension
   T1a   superficial tumor
   T1b   deep tumor
T2   Tumor more than 5 cm in greatest dimension
   T2a   superficial tumor
   T2b   deep tumor

*Regional Lymph Nodes (N)*
NX   Regional lymph nodes cannot be assessed
N0   No regional lymph node metastasis
N1*  Regional lymph node metastasis
*Note: Presence of positive nodes (N1) is considered stage IV.

*Distant Metastasis (M)*
MX   Distant metastasis cannot be assessed
M0   No distant metastasis
M1   Distant metastasis

**Histologic Grade (G)**

GX   Grade cannot be assessed
G1   Well differentiated
G2   Moderately differentiated
G3   Poorly differentiated
G4   Poorly differentiated or undifferentiated (four-tiered systems only)

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sarcoma, fibrosarcoma, leiomyosarcoma, and then malignant peripheral nerve tumor (7).

In general, although some sarcomas are clearly more aggressive than others, the specific histologic type appears to be of secondary importance in predicting the biologic behavior. This behavior is best predicted by the histologic grade, which is determined by 4 factors: mitotic index, degree of cellularity, necrosis when present, and degree of nuclear anaplasia.

## STAGING

The 2002 American Joint Committee on Cancer staging scheme for sarcomas is shown in *Table 3* (1). This staging system is like most tumor-node-metastasis (TNM) systems, but it also includes G for histologic grade. T1 tumors are ≤5 cm; T2, >5 cm. Both T1 and T2 tumors are designated a for superficial and b for deep. N0 indicates no disease-positive lymph nodes, while N1 indicates positive lymph nodes. With sarcoma, a positive lymph node is considered the same as any metastasis. M0 indicates no metastases; M1, distant metastases. The histologic grade varies somewhat depending on the institution. Some institutions use a 2-tiered system, designating low grade or high grade. Some use G1 for well differentiated, G2 for moderately differentiated, G3 for poorly differentiated, and G4 for more poorly differentiated or undifferentiated. Many institutions use a 3-tiered system.

Staging can be summarized as follows:
- Stage I—low-grade lesions without metastasis, regardless of the lesion's size or location
- Stage III—high-grade lesions that are large and deep
- Stage IV—lesions with metastasis (whether in a lymph node or a distant location), regardless of the lesion's size, location, or histologic grade

- Stage II—all other lesions

In the 1997 staging system, T2 lesions that were low grade were classified as stage IIa disease. Those lesions have been reclassified in the 2002 staging system and moved into stage I. This change reflects the observation that patients with large, deep, low-grade lesions have a better outcome than those with stage II lesions.

The staging systems for sarcoma remain controversial. One of the problems is the lack of specific staging for the tumor's location. Extremity, head and neck, visceral, and retroperitoneal sarcomas are all combined, so it is impractical to associate a stage with any kind of uniform surgical approach. Another problem is the failure to include biologic subtypes, some of which are much more aggressive than others. For example, synovial sarcomas and rhabdomyosarcomas are often very aggressive, and yet they may appear to be low-grade or small tumors. Conversely, well-differentiated liposarcomas and myxoid sarcomas have very low metastatic potential irrespective of their size.

The confusion is compounded by the fact that tumor behavior can vary considerably within a histologic subtype. An example is fibrosarcoma. The infantile version, even with a high

number of mitotic figures, tends to have very low metastatic potential compared with an adult fibrosarcoma of the same grade, which would be a fairly aggressive tumor.

## ETIOLOGY

In 1940, James Ewing, of Ewing's sarcoma fame, wrote: "Of the specific etiology of sarcoma, little is definitely known" (8). This is largely still true today, although some etiologic associations are known for a minority of sarcomas. These associated factors include genetic predisposition, exposure to radiation or chemical carcinogens, immunologic and viral factors, and environmental factors.

An association between trauma and soft tissue sarcoma has been suggested for over 200 years; in almost all instances, the relationship is probably not causal. Patients may report a history of trauma, but instead of causing the mass, the trauma probably directed their attention to it. Rare exceptions include dermatofibrosarcoma arising in a burn scar or fibrosarcomas arising at old orthopaedic fracture sites or in the surgical scars of patients with Gardner's syndrome. Gardner's syndrome is an inherited disorder characterized by clonic polyposis and multiple benign as well as some malignant neoplasms.

A genetic predisposition clearly exists in a minority of these tumors, such as Gardner's syndrome. Retinoblastoma is also associated with osteosarcomas, and this fact has led to the discovery that many sarcomas display structural defects of the *RB1* gene. Multiple endocrine neoplasia 2B syndrome includes ganglioneuromas, and patients with neurofibromatosis, or von Recklinghausen's disease, carry a 7% to 10% lifetime risk of developing malignant neurofibrosarcoma. Li-Fraumeni cancer family syndrome includes an increased susceptibility to a variety of sarcomas. Many patients with Li-Fraumeni syndrome have a defect in the p53 gene, and this tumor suppressor gene is defective in some types of sarcoma as well (9).

Ionizing radiation is associated with sarcoma and acts as both a tumor initiator and a promoter. Of the radiation-induced sarcomas, approximately 70% are malignant fibrous histiocytoma, which tends to be an aggressive type of tumor. The latency period is 7 to 25 years, and these patients typically have a poor prognosis. In one series of 53 patients, a 5-year survival rate of 26% was reported (10).

Chemical carcinogens have been reported to be etiologic agents. Although the effects of these carcinogens are much better described in experimental animals, the best human example is probably the dioxin-containing herbicide TDCC, or Agent Orange, a defoliant that was widely used in the Vietnam War. Agent Orange was implicated to such an extent that the Department of Veterans Affairs has agreed to compensate veterans who were exposed to it and developed sarcomas. Follow-up studies on the subject have yielded mixed results. Collins and coworkers found no causal relationship between dioxin exposure in factory workers and the incidence of sarcoma (11). However, Fingerhut et al (12) and Suruda et al (13) demonstrated a significant increase in risk of death from sarcoma among exposed factory workers.

Immunologic factors are implicated as well. Immunosuppression is associated with an increased risk of all kinds of neoplasms, typically those that are epithelial in origin (e.g., squamous cell carcinoma of the skin) and lymphomas. Sarcomas, however, also have been described.

Viral factors are clearly at play. In 1911, Peyton Rous demonstrated a transmissible avian sarcoma virus, named the Rous virus, and later won the Nobel Prize for this discovery. HIV is probably the best-known example in humans, being implicated in Kaposi's sarcoma. It is unclear, however, whether Kaposi's sarcoma is caused by the virus alone or by a combination of viral effect and immunologic suppression (probably the latter).

Other environmental factors are also to blame. The link between mesothelioma and asbestos is well known, as is the link between Stewart-Treves syndrome (postmastectomy lymphangiosarcoma) and long-standing lymphedema of the extremities. Interestingly, a risk of lymphangiosarcoma exists after mastectomy and radiation therapy even when the upper extremity appears grossly normal, and the tumor may not be in the irradiated field.

The link between foreign bodies and sarcoma has been described since the 1880s and has been well studied in rats. Rare human cases have also been described, involving surgical implants, plastic, bullets, surgical sponges, bone wax, or Teflon-Dacron prostheses. The largest study was done by Engel and colleagues, who looked at the rate of sarcoma in thousands of women with breast implants but did not find a statistically significant increase (14).

## DIAGNOSIS

The majority of patients with sarcoma present with a painless mass, although as many as 33% complain of pain, which may indicate a poor prognosis (7). Of the patients who present with pain, about half eventually undergo amputation; rapidly growing or aggressive tumor subtypes are more likely to be painful. Pain is often the first complaint in patients with malignant peripheral nerve tumors, which tend to spread along nerve bundles and are difficult to control.

Unfortunately, a prolonged delay in diagnosis is common. As many as half of patients wait for months to seek treatment for the mass, and the treating physician may entertain a diagnosis of a pulled muscle or traumatic hematoma for some time. These diagnoses should be considered only when there is a clear-cut history of trauma, and the physician should set a time limit of 6 to 8 weeks for observing the mass before treating it.

When evaluating a patient who has a potentially malignant mass, the physician should obtain these important elements of the history: 1) the duration of symptoms; 2) any recent change in size or consistency of the mass; 3) the constellation of symptoms, including pain, fever, or paresthesias; and 4) an antecedent history of trauma or other environmental factors, such as irradiation to the field, history of mastectomy, etc.

Six factors to assess in the physical examination include the location of the mass; its shape, size, consistency, and relation to surrounding tissues; and the state of the regional nodes. The nodes should be examined for metastasis even though the spread of sarcoma is almost always hematogenous.

In general, a biopsy should be performed on any soft tissue mass that is symptomatic or enlarging, any new mass that persists >4 weeks, or any soft tissue mass that is >5 cm in diameter.

The method of biopsy is critical and will vary somewhat, depending on the institution and the pathologist's experience.

Traditionally, closed biopsy techniques such as fine-needle aspiration (FNA) or core-needle biopsy (CNB) have had limited roles in diagnosing suspected sarcomas because of small sample size and questionable accuracy. The latter is particularly worrisome because of the highly pleomorphic nature of some sarcomas, which have a widely variable degree of malignancy throughout the mass. However, CNB and FNA are used routinely at some institutions, including M. D. Anderson Cancer Center and Memorial Sloan-Kettering Cancer Center, where a 1997 study reported a 93% adequacy rate and a 95% accuracy rate in determining malignancy (15). CNB is used by many surgeons at Baylor University Medical Center as well. Reliable use of this technique requires confidence on the part of the reviewing pathologist as well as a firm understanding of its limitations.

When open biopsy is preferred by the surgeon or pathologist, or if CNB/FNA returns an inadequate specimen, then excisional or incisional biopsy is required. For a small mass, 3 to 5 cm in its largest dimension, an excisional biopsy is appropriate. An incisional biopsy should be performed on masses >5 cm. Impeccable technique is critical: the surgeon must plan the biopsy with the intention of coming back for a major resection if the worst-case scenario, sarcoma, proves to be the diagnosis. The biopsy incision must be oriented along the long axis of the extremity, and a minimal amount of skin flap should be raised superficial to the incision. Meticulous hemostasis is essential to prevent the inadvertent dissemination of tumor cells.

In general, a diagnosis from frozen sections should be relied upon with extreme caution. Definitive treatment of a malignant lesion should be deferred until the results from the permanent sections and the results of an appropriate metastatic workup, including a computed tomography (CT) scan of the chest, have been reviewed. The lung is the most common site of metastasis for sarcomas, so a chest CT scan is typically indicated for all patients with newly diagnosed sarcoma. Other sites of metastasis vary by the type of lesion. An example would be angiosarcoma, which metastasizes to bone and thus may be an indication for a bone scan.

A preoperative imaging study is indicated in all cases of sarcoma, and both CT and magnetic resonance imaging (MRI) are used. Plain films are of limited overall value. In general, MRI is considered superior for studying soft tissues, but CT is widely used as well. The choice of imaging method is a function of the surgeon's preference and the experience of the institution's radiology staff.

## SURGICAL TREATMENT
Surgery is the mainstay of treatment for soft tissue sarcomas, and surgical interventions have spanned the spectrum from simple wide local excision to radical amputation. Early attempts at limited resection of these tumors resulted in uniformly poor results because of local recurrence, so radical amputation became the accepted surgical treatment.

In the past 2 decades, however, the pendulum has swung back in favor of limb-salvage techniques. With multimodal approaches, limb-sparing resections can be achieved, depending on the institution, in as many as 90% of patients, with an overall local recurrence rate of <10% (1). Compartment excision, one of the earliest limb-sparing techniques, was developed because of the potential for various tumors to spread microscopically along the muscle groups. The goal is to remove that group or groups of muscles from origin to insertion. Although simple wide local resection with adjuvant therapy has become the mainstay of limb-salvage techniques, there may still be a place for compartment excision. An example would be the presence of a small but otherwise aggressive tumor type located within a muscle group whose excision can afford a cure, such as the adductor of the thigh or the quadriceps.

Compartment excision requires that the surgeon identify 3 things before marking the incisions: 1) the location of the old biopsy incision, 2) the presumed extent of the tumor, and 3) where skin flaps should be. As with the biopsy, the surgeon should carefully avoid touching the tumor itself, try to manipulate tissues around the tumor without ever exposing the tumor, and keep a 3-cm margin if possible. When this is not feasible due to the deep margin, the surgeon should try to always get at least one uninvolved fascial plane.

For a wide local excision, the incisions are based on the extent of the tumor plus at least a 3-cm margin, without any particular anatomic landmarks. Again, the surgeon must pay meticulous attention to hemostasis, try not to touch the tumor, and get 3- to 5-cm margins all the way around. If necessary, involved major vascular structures, which should have been revealed by the preoperative imaging studies, can be resected and then replaced with interposition grafts. The previous biopsy site should be included in any resection. This includes the previous scar for incisional or excisional biopsies and the puncture site and entire needle tract for FNA or CNB.

Contraindications to limb-sparing techniques include instances in which an underlying defect persists through the entire extremity, as in the Stewart-Treves syndrome. In the case of lymphangioma arising from lymphedema, it makes no sense to simply resect the tumor and leave other at-risk tissue behind. The same concept holds true for malignant schwannomas in a patient with neurofibromatosis. These patients are candidates for amputation. Recurrence alone, however, is not an indication for amputation when these patients can undergo additional wide local excision.

Amputation is also indicated when resection will not leave an anatomically functional limb. Some proximal extremity lesions require amputation. A lesion in the very proximal arm may require forequarter amputation; likewise, a lesion in the proximal thigh or groin may require hemipelvectomy or hip disarticulation. More distal lesions can be cured with limited amputation, such as a transmetatarsal amputation for a lesion in the toe or a digital ray amputation for a lesion in a finger or hand.

## ADJUVANT THERAPY
Adjuvant therapy is important even though surgical excision is the mainstay of treatment. For small, low-grade tumors, wide local excision alone provides very good results. Most patients, however, will go on to receive either external-beam radiation therapy (EBRT) or perioperative brachytherapy from an implanted source. Patients with low-grade lesions >5 cm in diameter are typically offered EBRT. Patients with high-grade lesions between 5 and 10 cm in diameter can be given either EBRT or brachytherapy. Patients with very large (≥10 cm), high-grade le-
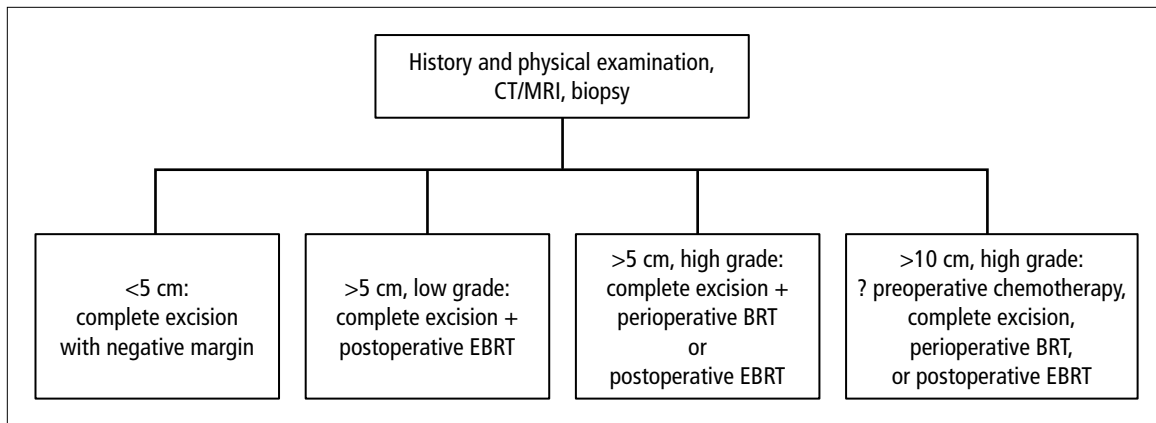
**Figure.** Algorithm for diagnosis and treatment of soft tissue sarcoma of the extremities developed at Memorial Sloan-Kettering Cancer Center. Reprinted with permission from reference 7. CT indicates computed tomography; MRI, magnetic resonance imaging; EBRT, external-beam radiation therapy; BRT, brachytherapy.

**Table 4. Five-year survival rates in extremity soft tissue sarcoma***

| Stage | N | Freedom from local recurrence | Disease-free survival | Overall survival |
|---|---|---|---|---|
| I | 137 | 88.04% | 86.13% | 90.00% |
| II | 491 | 81.97% | 71.68% | 80.89% |
| III | 469 | 83.44% | 51.77% | 56.29% |

*Local recurrence, disease-free survival, and overall survival by stage. Source: Memorial Sloan-Kettering Cancer Center for the time period of 7/1/82 to 6/30/00. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual, Sixth Edition* (2002) published by Springer-Verlag New York, www.springer-ny.com.

sions are considered for neoadjuvant therapy with chemoradiation—a radiation sensitizer and either EBRT or brachytherapy. The radiation sensitizer is usually doxorubicin or ifosfamide based.

Adjuvant therapy using doxorubicin- or ifosfamide-based regimens is still somewhat controversial, largely because the survival benefit has not been uniform from center to center (1). Exceptions include rhabdomyosarcoma and Ewing's sarcoma, which are very sensitive to and should be treated with adjuvant chemotherapy. Isolated limb perfusion therapy using cytotoxic agents such as melphalan, tumor necrosis factor, and interferons holds great promise but remains investigational (16).

The *Figure* illustrates a treatment algorithm proposed by the Memorial Sloan-Kettering Cancer Center group, starting with history, physical examination, preoperative imaging study (CT or MRI), and biopsy (7). Small lesions are treated with complete excision, as long as a negative margin can be obtained. Depending on their size and histologic grade, larger lesions are treated with various combinations of complete excision and pre- or postoperative radiation therapy and, for very large lesions, neoadjuvant chemoradiation.

## OUTCOME AND FOLLOW-UP

*Table 4* shows outcome data from Memorial Sloan-Kettering Cancer Center from the period 1982 to 2000. Reasonably good results were reported for stage I tumors, with a disease-free survival rate of 86% and freedom-from-recurrence rate of 88%. The rates for stage III lesions go down to about 52% and 83%, respec-

tively. Data for stage IV lesions are not shown, probably because they are uniformly dismal.

Regular follow-up is very important for these patients, at least annually if not more frequently for the first 5 years. The follow-up for high-grade lesions should be directed at both local recurrence and metastatic disease, whereas local recurrence is the primary concern for low-grade lesions. Follow-up must be continued for the long term, as low-grade lesions can recur as late as 20 years after the original resection. In fact, patients who are clear of disease 5 years after resection still have a 10% risk of local recurrence (17).

Local recurrence is not a death sentence in extremity sarcoma as it often is in retroperitoneal sarcoma. These patients can still be treated with limb-salvage methods when technically feasible, and the survival rate approaches that of previously untreated patients. Pulmonary metastases—even multiple or bilateral metastases—are typically resected, and aggressive resection is associated with a cure in 25% to 35% of patients (1).

Patients with unresectable metastases or extrapulmonary metastases are offered adjuvant chemotherapy. Occasionally, patients with bony or cerebral metastases are offered palliative EBRT.

## CONCLUSION

Soft tissue sarcomas of the extremities are rare and challenging neoplasms, and every general surgeon is likely to face one at least once or twice in his or her career. Recurrence of extremity sarcoma is not a death sentence, and these patients should be treated aggressively. When providing definitive therapy, the general surgeon should involve colleagues from appropriate related services (e.g., orthopaedics, vascular surgery, plastic surgery, oncology, radiation therapy) early in the process. Prompt diagnosis and the appropriate choice of biopsy method are vital in treating a potentially malignant soft tissue mass.

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